

Memorandum:

To File: BLA 97-1251
From: Lauren E. Black, Ph.D., Reviewing Pharmacologist
Through: M. David Green, Ph.D., Branch Chief, Clinical Pharmacology and Toxicology Branch
Subject: Pharmacology Review of the basiliximab BLA
Product: **Simulect**,
(basiliximab) chimeric (human/murine) IgG1 for use renal allograft rejection
Sponsor: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
Date: 3/23/98

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LRS 5/12/98
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BACKGROUND:

The main point of animal studies conducted using basiliximab (Simulect or SDZ CHI 621) was to identify clinical safety concerns to support the clinical safety of the drug as used as part of the post surgical immunosuppressive drug regimen to prevent renal allograft rejection. Additional toxicity studies were conducted to evaluate the drug's reproductive toxicity potential as administered in cynomolgus monkeys during organogenesis.

Dosing of primates did evoke minor immunogenic antibody production, but higher, saturating doses were demonstrated to achieve supraclinical drug levels, 100% receptor saturation of IL-2 receptor sites, and little to no monkey anti chimeric antibody responses.

Simulect binds to the Interleukin-2 receptor with high affinity, and is capable of blocking endogenous IL-2 binding. Potency and activity in these assays has been demonstrated in numerous preclinical literature reports, supplied with the BLA. In vitro binding profiles of basiliximab to lymphocytes from humans as well as cynomolgus and rhesus monkeys, were superimposable, indicating that either monkey species was a relevant one for use in toxicity studies. Therefore, the toxicology studies were adequately designed to evaluate clinical safety concerns as evaluated in relevant animal species under controlled conditions.

PRECLINICAL STUDIES:

In general, the appropriate studies for preclinical safety were conducted by the sponsor to support the currently approved dosing in patients.

Toxicology studies mainly consisted of 2 studies performed using intravenous dosing and repeated (twice weekly) administration for periods of up to 28 days in rhesus monkeys, at doses in the range of 1-5 mg/kg. Cynomolgus monkeys were used in the reproductive toxicity study of embryo-fetal development. Dosing was conducted every 4 days during days 20 to 48 of pregnancy, the monkey equivalent of a human first trimester, the active period of organogenesis. No abnormalities in fetal development were observed when the fetuses were examined at day 100 of gestation, a standard time of sacrifice for monkey reproductive evaluations when fetal development should be complete, but prior to the end of gestation.

Compared with clinical pharmacology data, drug levels achieved in monkey serum (including pregnant monkeys) were similar to or approximately 10-fold higher than the levels achieved in patients using the recommended regimen.

There were no animal toxicity results attributable to drug, and which would indicate clinical safety concerns, nor any findings which would require special warnings in the label, or otherwise affect the current course of product development. Full studies, conducted according to good laboratory practices, were conducted appropriately, and included in their design all veterinary clinical endpoints, including hematologic, clinical chemistry, ophthalmologic, histopathologic, clinical, and electrocardiographic evaluations.

Results of the pharmacokinetic, pharmacology and toxicology studies were summarized accurately and succinctly by the sponsor. The summaries are supplied here as an attachment. The sponsor has completed an adequate preclinical program to best inform the clinical use of the product, and no further studies are required in phase 4.

PRODUCT LABELING:

The following remarks (regarding the preclinical data used in drug labeling) were circulated for comment and have been incorporated into the label of the product. Sections from the label are reproduced below from the memorandum composed for the labeling internal meeting in April 1998.

Carcinogenesis, Mutagenesis and Impairment of Fertility: "No mutagenic potential of Simulect was observed in in vitro assays with Salmonella (Ames) and V79 Chinese hamster cells. No long-term or fertility studies in laboratory animals have been performed to evaluate the potential of Simulect to produce carcinogenicity or fertility impairment, respectively."

Comment: There is no objection to the sponsor's wording.

Pregnancy: "Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. However, no maternal toxicity, embryotoxicity or teratogenicity was observed in cynomolgous monkeys 100 days post coitum following intravenous bolus injections of up to 5 mg/kg basiliximab administered twice weekly during the organogenesis period. Because IgG molecules are known to cross the placental barrier, and because animal reproduction studies are not always predictive of human response, Simulect should only be used in pregnant women when the potential benefit justifies the potential risk to the fetus. Women of childbearing potential should use effective contraception before beginning Simulect therapy, during therapy, and for 2 months after completion of Simulect therapy".

Comment: There is no objection to the sponsor's wording, however, we would request the change to read "...in cynomolgus monkeys 100 days post coitum following dosing with basiliximab during the organogenesis period; blood levels in pregnant monkeys were 13 X higher than those typically seen in human patients." On discussion 4/24/98, the committee found this acceptable.

Nursing Mothers: "It is not known whether Simulect is excreted in human milk. Because many drugs including human antibodies are excreted in human milk, and because of the potential for adverse reactions, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother."

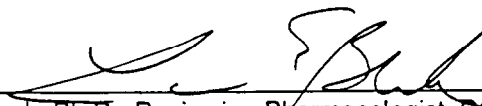
Comment: There is no objection to the sponsor's wording.

In summary, only a minor change to the sponsor's proposed toxicology labeling is recommended based on review of the file. These changes have been accepted by Novartis and incorporated into the label.

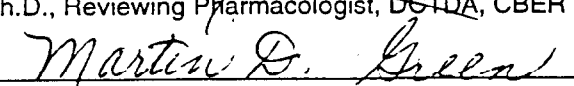
Conclusions:

Based on review of the pharmacology and toxicology data, the safety of Simulect is adequately supported, and no objection is offered to approving this licensing application.

REVIEWER:

 5/12/98
Lauren E. Black, Ph.D., Reviewing Pharmacologist, DCTDA, CBER

CONCURRENCE:

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